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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/334,325	06/16/1999	STEWART A. CEDERHOLM-WILLIAMS	CV0276A	5209

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/12/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/334,325	Stewart Cederholm-Williams
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 5, 2002*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, and 13-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, and 13-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s). _____
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____	6) ☐ Other:

DETAILED ACTION

Applicant's appeal brief filed 12-5-02 has been entered. In view of the appeal brief filed 12-5-02, the finality of the Official action mailed 6-5-02 (Paper No. 18) has been withdrawn.

Claims 1, 2 and 13-16 are pending and under consideration.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See M.E.P.. §§ 602.01 and 602.02.

The oath or declaration is defective because:

The priority of provisional applications 60/083,571 and 60/089,543 should be claimed under 35 U.S.C. 119(e) section not under 35 U.S.C. 120. Further, if priority of provisional application 60/083,571 is not intended to be claimed, it should be removed from the oath/declaration.

Priority

2. If applicant desires priority under 35 U.S.C. 119 (e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The benefit of provisional application 60/083,571, filed

4-30-98, has been claimed in Oath/Declaration but the claimed priority has not been mentioned at the first sentence of the specification following the title. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is unclear whether the steps of the method as claimed are sequential as recited or the steps could be in any order. If the steps could be in any order, then when adhering a pliable, adhesive fibrin gel to the cell, there is no nucleic acid on the cell to be trapped by the fibrin gel and no transformation of the cell by nucleic acid.

The phrase "wherein nucleic acid is applied in admixture with a fibrin or fibrinogen composition...fibrin gel" in claim 2 is vague and renders the claim indefinite. Claim 1 requires nucleic acid and fibrin gel are added separately, however, claim 2 requires nucleic acid and fibrin composition that form fibrin gel are added in admixture. Claim 2 depends on claim 1 but claim 2 reads on a method having totally different method steps from claim 1. Claim 2 improperly depends on claim 1 and it is unclear what is intended to be claimed in claim 2.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transforming a cell *in vivo* as taught by Donovan et al., 1998 (US Patent No. 5,833,651), does not reasonably provide enablement for a method of transforming a cell *in vivo* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell with apparatus other than stent or balloon catheter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 2 and 13-16 are directed to a method of transforming cells by applying nucleic acid, such as a plasmid or the nucleic acid is incorporated in a virus, and fibrin gel to the cells separately, or applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells. The claims read on combining a fibrin gel with any vector or virus carrying the nucleic acid to transform cells *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc.

The specification discloses the preparation of preferred sealant compositions and the incorporation of nucleic acid into fibrin gel, but fails to provide an enabling disclosure for the method of using fibrin monomer or fibrinogen that forms fibrin gel for genetic transformation of

any nucleic acid or virus containing said nucleic acid at any location of a subject *in vivo*. The specification fails to provide adequate guidance and evidence for transforming cells *in vivo* via the combination of a nucleic acid, a vector or a virus with a fibrinogen composition or a fibrin gel. No teachings are present within the specification in regard to how to transform cells in a subject with any nucleic acid in any vector or any virus containing said nucleic acid by using fibrinogen composition or fibrin gel.

The claims read on gene therapy *in vivo*. The state of the art for gene therapy *in vivo* was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target

(page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to transform a cell *in vivo* with any nucleic acid and a pliable, adhesive fibrin gel via various administration routes so as to provide therapeutic effects in an individual.

The specification also fails to provide adequate guidance and evidence for how to administer a pliable, adhesive fibrin gel either mixed with a nucleic acid or separate from a nucleic acid to a subject such that target cells in said subject are transformed with said nucleic acid. The specification fails to provide adequate guidance what apparatus is used to deliver the pliable, adhesive fibrin gel to target cells in a subject for transformation of said cells. It was known in the art that the pliable, adhesive fibrin gel will polymerize quickly. The specification indicates that "Generally, the sealant mixture remains conveniently pliable for about 30 seconds or less" (page 17, lines 16, 17). When the nucleic acid is administered after the pliable, adhesive fibrin gel has been administered to target cells, the nucleic acid might not be trapped in the fibrin gel because the pliable, adhesive fibrin gel will polymerized in a short period of time and the target cells could not be transformed with said nucleic acid. There is no evidence of record that shows transformation of target cells in a subject with any nucleic acid via administering the pliable, adhesive fibrin gel and the nucleic acid in a mixture or administering said fibrin gel and nucleic acid in a sequential order. Further, the specification fails to provide adequate guidance and evidence how to transform the target cells at various locations inside the body of a subject rather than on the surface of said subject with a nucleic acid and a pliable, adhesive fibrin gel. Since the pliable, adhesive fibrin gel will polymerize in a short period of time, one would require

to deliver said fibrin gel to target cells at various locations in a subject before polymerization of said fibrin gel so as to transform said target cells with a nucleic acid. However, the specification fails to provide adequate guidance for such delivery and one skill in the art at the time of the invention would not know how to use the claimed pliable, adhesive fibrin gel to transform target cells with a nucleic acid at various locations in a subject.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicant argues that the specification teaches how to make the transforming composition and that transforming nucleic acids are well-known and one of ordinary skill knows how to measure transformation (brief, bridging pages 4, 5). This is not found persuasive because of the reasons set forth above.

Applicant argues that the 35 U.S.C. 112 first paragraph enablement rejection is related to 35 U.S.C. 101 rejection and the Office does not fulfill Utility Examination Guidelines (brief, pages 5-8). This is not found persuasive because the 35 U.S.C. 112 first paragraph enablement rejection is **not** a 35 U.S.C. 101 rejection, therefore, applicant's argument regarding the 35 U.S.C. 101 rejection is irrelevant. The claimed invention is not enabled because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2 and 13-16 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Donovan, 1998 (US patent No. 5,833,651).

Claims 1, 2 and 13-16 are directed to a method of transforming cells by applying nucleic acid, such as a plasmid or the nucleic acid is incorporated in a virus, and fibrin gel to the cells

separately, or applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells. Claims 15 and 16 specify mixing a fibrin monomer composition with a polymerizing agent preparation effective to convert the fibrin monomer into a fibrin gel.

Donovan teaches a method for delivering nucleic acid to cells accessible from a wall of a body lumen comprising providing a stent having a lumen-wall contacting surface, a lumen-exposed surface, a first polymer composition comprising fibrin covering at least a portion of the lumen-wall contacting surface to form a polymer covered stent, and a virus to deliver nucleic acid to a cell wherein the virus is associated with the first polymer composition covering the lumen-wall contacting surface, and positioning said stent in a lumen of the body to deliver said nucleic acid to said cell. Donovan also teaches using a second polymer composition comprising fibrin to cover at least a portion of the first polymer composition on the lumen-wall contacting or lumen-exposed surface of the stent (e.g. column 3, 4, 20). Donovan constructed plasmid pCMVhpAP expressing the reporter hpAP gene under the control of CMV promoter and an E1 deleted recombinant adenoviral vector ADVhpAP expressing hpAP, and prepared a fibrin covered stent which was placed in a solution of plasmid or virus overnight to load the plasmid or virus into the fibrin covered stent for determining whether fibrin enhances gene delivery to the artery (e.g. column 18, 19, 20). Donovan further teaches mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell (e.g. column 13).

Claim 2 specifies the nucleic acid is applied in admixture with a fibrin or fibrinogen composition that form a pliable, adhesive fibrin gel. Claim 1 does not specify the sequential steps of applying the nucleic acid and the pliable, adhesive fibrin gel. Further, mixing a solution of fibrin monomer and virus containing nucleic acid would form a pliable and adhesive fibrin gel before the gel become not pliable and applying a nucleic acid to cells before, during, or after the formation of a pliable, adhesive fibrin gel is for the purpose of entrapping the nucleic acid in fibrin gel, i.e. the function of the fibrin gel is to hold the nucleic acid, so as to deliver said nucleic acid to said cells. Therefore, claims 1, 2 and 13-16 are either anticipated by or in alternative are obvious over Donovan.

Applicant argues that the term "fibrin monomer" of the present application is different from the term "fibrin monomer" in Donavan (brief, page 9). This is not found persuasive because the term "fibrin monomer" defined in the present application means fibrin that is held in soluble form and prevented from clotting by using agent such as acid and it was well known in the art how to prevent fibrin monomer from polymerization by using acid pH. Further, the term "fibrin monomer" recited by Donovan means "**fibrin monomer**" that is not polymerized and one of ordinary skill in the art at the time of the invention would know how to maintain fibrin monomer from polymerization. Thus, the term "fibrin monomer" recited in the present application has the same meaning as the term "fibrin monomer" recited by Donovan.

Applicant argues that there is no motivation to entrap nucleic acid in a pliable fibrin gel adhered to a cell and cites Winner, 202 F.3d 1340, 53 USPQ2d 1580 regarding club-like

automobile anti-theft device (brief, pages 9, 10). This is not found persuasive because the claims not only read on entrapping nucleic acid adhered to a cell in a pliable fibrin gel but also encompass mixing the nucleic acid with a fibrin composition before applying to the cell and Donovan indeed teaches mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell. In Winner, there are three references used, however, there is only one reference cited under the 35 U.S.C. 102/103 rejection in the present application, thus, Winner is not applicable to the present application. Further, applying a nucleic acid to cells before, during, or after the formation of a pliable, adhesive fibrin gel is for the purpose of entrapping the nucleic acid in fibrin gel, i.e. the function of the fibrin gel is to hold the nucleic acid, so as to deliver said nucleic acid to said cells and thus, is obvious for one of ordinary skill in the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

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